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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/393,844	09/10/1999	KATHERINE A. HIGH	10650/002002	3411

7590 02/06/2006

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/393,844	HIGH ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2005 and 22 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3 and 6-9* is/are rejected.

7)☐ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is a reply to the Papers filed 5 October 2005 and 22 November 2005 in response to the Non-Final Office Action mailed 1 April 2005. Claims 1-4 and 6-9 were considered in the 1 April Office Action. Claims 7 and 9 were amended in the 5 October Paper. Claims 1-4 and 6-9 are presently pending and under examination.

Response to Amendment and Arguments

Notice To Comply With Sequence Rules

The filing of a substitute paper copy of the sequence listing and CRF, which corrects the defect identified therein, is acknowledged. However, the submission fails to include a statement directing entry of the paper copy of the sequence listing into the specification (see the "notice to comply" attached to the 1 April Office Action). A reply to this Office Action should include a statement referring to the paper copy filed 15 October 2005 and directing its entry into the specification.

Claim Rejections - 35 USC § 102 and 103

Rejection of claims 1 and 6-9 under 35 U.S.C. 102(e) as being anticipated by Wilson *et al.* US Patent No. 5,866,552 and rejection of claims 1-3 and 7 under 35 U.S.C. 103(a) as being unpatentable over Wilson *et al.* (*supra*) in view of Wang *et al.* (1996) *Hum. Gene Ther.* 7:1743-1756 as evidenced by Kurachi *et al.* (1995) *J. Biol. Chem.* 270:5276-5281 is withdrawn in view of the showings of the Declaration under 1.131 filed 22 November 2005, which showings are

sufficient to antedate the Wilson *et al.* reference, and in view of the amendments to claims 7 and 9.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* (1993) *Nat. Genet.* 5:397-402 in view of Skulmowski *et al.* (1995) *Method. Mol. Genet.* 7:3-12.

Claim 1 is directed to a composition comprising a virus, said virus comprising a recombinant AAV vector comprising at least two AAV inverted terminal repeats, a promoter/regulatory sequence, an isolated DNA encoding Factor IX and accompanying 5' and 3' untranslated regions and a transcription termination signal.

In the section entitled, "Construction of recombinant adenoviral vectors" commencing in the left column on page 401, Smith *et al.* teaches a virus to be used for delivering a gene encoding Factor IX into cells *in vivo* for gene therapy, which virus comprises a promoter/regulatory sequence, an isolated DNA encoding Factor IX and accompanying 5' and 3' untranslated regions (see the sentence bridging the left and right columns on page 401) and an SV40 early polyadenylation site. Smith *et al.* does not teach an AAV vector comprising at least two AAV inverted terminal repeats.

Skulimowski *et al.* teaches a composition comprising a virus comprising an AAV vector comprising two AAV inverted terminal repeats (see especially Figure 2(B) and the caption thereto, and Figure 3 and the caption thereto), which virus Skulimowski *et al.* teaches, "[has] unique features that make this virus attractive for gene therapy include[ing] the facts that AAV is prevalent in humans, it has never been identified as a causative agent of human disease, and it is able to insert its genome locus-specifically into human chromosomes" (Introduction, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the AAV vector of Skulimowski *et al.* for the adenoviral vector of Smith *et al.* to produce a composition comprising a virus according to the limitations of the instant claim 1.

Motivation to combine these teachings is found in the nature of the problem to be solved by the composition of Smith *et al.*, which is intended to deliver an expressible Factor IX gene into cells *in vivo* to treat hemophilia (see especially the paragraph bridging the left and right columns on page 397), and the limitations of adenoviral vectors as stated in the teachings of Smith *et al.* In particular, Smith *et al.* found that expression of Factor IX was transient, which Smith *et al.* teaches was likely due, at least in part, to a loss of vector DNA (see especially Figure 3 and the caption thereto and the paragraph bridging pages 400-401). Smith *et al.* further teaches that the transient nature of Factor IX expression when delivered by adenovirus necessitates repeated administration of the vector; however, attempts to administer a second dose of virus were ineffective (see especially the first full paragraph on page 401). In view of these limitations, the skilled artisan would be motivated to substitute the AAV vector of Skulimowski *et al.* for the adenovirus vector of Smith *et al.* because, as Skulimowski *et al.* teaches, "Most of these viral vectors [referring to adenovirus among others] express the introduced gene transiently, with the exception of retroviruses and AAVs, which have the ability to integrate into the cellular chromosome" (Introduction, paragraph 2).

In view of the fact that Smith *et al.* specifically teaches that transient expression due to, at least in part, a loss of vector DNA is a problem to be overcome in developing reagents, one of ordinary skill in the art would clearly be motivated to substitute the AAV vector of Skulimowski

et al. in order to obtain the expected benefit of integration of the vector into the genome and more stable expression.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because Skulimowski *et al.* provides detailed instruction as to how to make a virus comprising an AAV vector and Smith *et al.* provides detailed instruction as to how to construct a Factor IX transgene.

In view of these considerations, the composition comprising a virus of independent claim 1, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

In addition, all of the limitations of dependent claims 6-9 are also found in the teachings of Smith *et al.* and Skulimowski *et al.* and would also have been obvious to the skilled artisan for the reasons set forth herein above. Specifically, Smith *et al.* teaches the composition for delivery of the virus into an animal *in vivo*, which composition would comprise a pharmaceutically acceptable carrier according to claim 6; Skulimowski *et al.* teaches the expression cassette of the AAV comprises a CMV promoter according to claim 7 (see especially Figure 2(B)); and he Factor IX gene of Smith *et al.* comprises an SV40 polyadenylation (*i.e.*, transcriptional termination) signal according to claim 8 (see especially the fourth full paragraph on page 401, lines 24-26). Finally, as any composition comprised in a container can reasonably be construed as a "kit" and Skulimowski *et al.* contemplates aliquoting virus in tubes (Figure 3), the kit comprising the virus of claim 1 recited in claim 9 would be obvious for the reasons set forth herein above.

Thus, the composition of claims 1 and 6-9, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the teachings of Smith *et al.* and Skulimowski *et al.* Therefore, the claims are properly rejected under 35 USC §103(a). It is noted that the declaration under 35 USC §1.131 cannot be used to overcome the instant rejection because both Smith *et al.* and Skulimowski *et al.* were published more than one year prior to the effective filing date of the instant claims.

Claims 1 and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyanohara *et al.* (1992) *New Biol.* 4:238-246 in view of Skulmowski *et al.* (1995) *Method. Mol. Genet.* 7:3-12.

The limitations of claim 1 are described herein above. In the section entitled, "*Construction and Preparation of HSV-1 Vectors*" commencing in the left column on page 244 and in Figure 1 and the caption thereto, Miyanohara *et al.* teaches a virus to be used for delivering a gene encoding Factor IX into cells *in vivo* for gene therapy, which virus comprises a promoter/regulatory sequence, an isolated DNA encoding Factor IX and an SV40 early polyadenylation site (see especially the caption of Figure 1). Although Miyanohara *et al.* does not explicitly teach that the vector used in the method should comprise "accompanying 5' and 3'" untranslated sequence, this limitation, as it is understood, is inherent to the expression cassette of Miyanohara *et al.* There is no definition of "accompanying 5' and 3' untranslated region" that would exclude any sequence expressed from the vector that is not translated from the 5' and 3' untranslated region of the claims. As described above, the vector of Miyanohara *et al.* comprises a polyadenylation signal, which would be 3' untranslated sequence, and all

eukaryotic genes must comprise 5' untranslated sequence upon which the ribosome assembles in order for translation to occur. Thus, absent evidence to the contrary, the expression cassette of Miyanohara *et al.* comprises "accompanying 5' and 3' sequence". Therefore, Miyanohara *et al.* teaches all of the limitations of the expression cassette of the claims but does not teach an AAV vector comprising at least two AAV inverted terminal repeats.

Skulimowski *et al.* teaches a composition comprising a virus comprising an AAV vector comprising two AAV inverted terminal repeats (see especially Figure 2(B) and the caption thereto, and Figure 3 and the caption thereto), which virus Skulimowski *et al.* teaches, "[has] unique features that make this virus attractive for gene therapy include[ing] the facts that AAV is prevalent in humans, it has never been identified as a causative agent of human disease, and it is able to insert its genome locus-specifically into human chromosomes" (Introduction, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the AAV vector of Skulimowski *et al.* for the HSV vector of Miyanohara *et al.* to produce a composition comprising a virus according to the limitations of the instant claim 1.

Motivation to combine these teachings is found in the nature of the problem solved by the composition of Miyanohara *et al.*, which is intended to be used to deliver an expressible Factor IX gene into cells *in vivo* to treat hemophilia (see especially the paragraph bridging the left and right columns on page 397), and the limitations of HSV vectors as stated in the teachings of Miyanohara *et al.* In particular, Miyanohara *et al.* found that expression of Factor IX was transient (see especially Figure 5 and the caption thereto) and that cytotoxicity is a problem

associated with the use of HSV vectors (see especially page 243, column 2, lines 5-21). In view of these limitations, the skilled artisan would be motivated to substitute the AAV vector of Skulimowski *et al.* for the HSV vector of Miyanohara *et al.* because, as Skulimowski *et al.* teaches, "Most of these viral vectors [referring to herpesvirus among others] express the introduced gene transiently, with the exception of retroviruses and AAVs, which have the ability to integrate into the cellular chromosome" (Introduction, paragraph 2) and "AAV is attractive as a gene therapy vector, primarily because of its classification as a nonpathogenic human virus that can stably integrate into the host cell chromosome" (second full paragraph on page 10).

In view of the fact that Miyanohara *et al.* specifically teaches that transient expression and cytotoxicity are problems to be overcome in developing vectors for delivery of Factor IX, one of ordinary skill in the art would clearly be motivated to substitute the AAV vector of Skulimowski *et al.* in order to obtain the expected benefit of improved safety due to the nonpathogenic nature of the virus and integration of the vector into the genome for more stable expression.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because Skulimowski *et al.* provides detailed instruction as to how to make a virus comprising an AAV vector and Miyanohara *et al.* provides detailed instruction as to how to construct a Factor IX transgene.

In view of these considerations, the composition comprising a virus of independent claim 1, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

In addition, all of the limitations of dependent claims 6-9 are also found in the teachings of Miyanohara *et al.* and Skulimowski *et al.* and would also have been obvious to the skilled artisan for the reasons set forth herein above. Specifically, Miyanohara *et al.* teaches the composition for delivery of the virus into an animal *in vivo*, which composition would comprise a pharmaceutically acceptable carrier according to claim 6; both Skulimowski *et al.* and Miyanohara *et al.* teach an expression cassette comprising a CMV promoter according to claim 7; and the Factor IX gene of Miyanohara *et al.* comprises an SV40 polyadenylation (*i.e.*, transcriptional termination) signal according to claim 8 (see especially Figure 1 and the caption thereto). Finally, as any composition comprised in a container can reasonably be construed as a "kit" and Skulimowski *et al.* contemplates aliquoting virus in tubes (Figure 3), the kit comprising the virus of claim 1 recited in claim 9 would be obvious for the reasons set forth herein above.

Thus, the composition of claims 1 and 6-9, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the teachings of Miyanohara *et al.* and Skulimowski *et al.* Therefore, the claims are properly rejected under 35 USC §103(a). It is noted that the declaration under 35 USC §1.131 cannot be used to overcome the instant rejection because both Miyanohara *et al.* and Skulimowski *et al.* were published more than one year prior to the effective filing date of the instant claims.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* (*supra*) in view of Skulmowski *et al.* (*supra*) or Miyanohara *et al.* (*supra*) in view of Skulmowski *et al.* (*supra*) as applied to claim 1 herein above and further in view of Kurachi *et al.* (1995) *J. Biol. Chem.* 270:5276-5281.

The limitations of claim 1 and the teachings of Smith *et al.* in view of Skulmowski *et al.* and Miyanohara *et al.* in view of Skulmowski *et al.* are described herein above.

Claim 2 limits the virus of claim 1 to comprising a portion of intron 1 of a Factor IX gene and claim 3 further limits the portion of intron 1 to about 0.3 to about 1.7 kb in length.

Neither Smith *et al.* nor Miyanohara *et al.* teach that the Factor IX expression cassette described therein should comprise a portion of intron 1 of a Factor IX gene.

Kurachi *et al.* teach inclusion of portions of the Factor IX gene intron 1 in Factor IX expression cassettes significantly increased the level of Factor IX produced by hepatocytes (see especially Table II and the first full paragraph on page 5280). In particular, Kurachi *et al.* teaches that a cassette comprising a 1.4 kb portion of the Factor IX intron 1 (see especially the description of FIXm1 in Figure 2 and the caption thereto) provided the highest level of expression (Table II).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Factor IX expression cassettes taught by Smith *et al.* or Miyanohara *et al.* to include a 1.4 kb portion of Factor IX as taught by Kurachi *et al.* according to the limitations of the instant claims 2 and 3.

Motivation to combine these teachings is found in the nature of the problem to be solved by the expression cassettes of Smith *et al.* or Miyanohara *et al.*, which is to provide high-level expression of Factor IX, and the teaching of Kurachi *et al.* that the inclusion of a 1.4 kb portion of the Factor IX intron 1 dramatically increases Factor IX expression.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because Kurachi *et al.* teaches that the enhancement of expression by

intron 1 appears to be through a general mechanism of increasing mRNA stability (see especially the paragraph bridging the left and right columns on page 5280). Thus, one would expect that the effect of the intron would be independent of the promoter or other elements used in the expression cassette.

In view of these considerations, the invention of claims 1-3, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art. It is noted that the declaration under 35 USC §1.131 cannot be used to overcome the instant rejection because all of the references used in making the rejection were published more than 1 year prior to the effective filing date of the instant claims.

Allowable Subject Matter

Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER